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AUTHOR(S):

Kajiwara, Mitsuru; Mutaguchi, Kazuaki

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CLINICAL EFFICACY AND TOLERABILITY OF GOSHA-JINKI-GAN, JAPANESE TRADITIONAL HERBAL MEDICINE, IN FEMALES WITH OVERACTIVE BLADDER

Mitsuru KAJIWARA and Kazuaki MUTAGUCHI

The Department of Urology, Nakatsu Daiichi Hospital

The efficacy and tolerability of a single-agent treatment with 7.5 g/day Gosha-jinki-gan in Japanese females with overactive bladder were analyzed objectively with linguistically validated questionnaires. A total of 44 Japanese females diagnosed as having overactive bladder were enrolled. Before and after the treatment, urinary frequency during the daytime and sleep was counted for two days, and the International Prostate Symptom Score index scores and quality of life index scores were examined. The efficacy assessment was done by comparing the quality of life index scores. The total scores of International Prostate Symptom Score, quality of life index scores and urinary frequency during the daytime and sleep were significantly decreased, respectively. Objective evaluation with the quality of life questionnaire yielded a result of excellent in 7%, improved in 46%, unchanged in 41% and worsened in 7%. Adverse reactions were observed in 9%. Gosha-jinki-gan could be a safe and effective potential therapeutic alternative in females with overactive bladder.

(Hinyokika Kiyo **54**: 95–99, 2008)

Key words: Gosha-jinki-gan, Overactive bladder

INTRODUCTION

Overactive bladder (OAB) is a symptom syndrome that consists of urgency, with or without urge incontinence, usually with frequency and nocturia¹⁾. The incidence of OAB in middle-aged and older adults is reported to be 12.4% in Japan²⁾ and 16.5% in Europe³⁾. The incidence of OAB gradually increases with age, and OAB greatly affects the quality of life (QOL)⁴⁾; therapeutic intervention becomes necessary. Treatment options for OAB range from behavioral modification such as bladder training through medical treatment with drugs. Anticholinergic drugs are generally the most frequently prescribed options for females with the storage symptoms attributable to OAB. Gosha-jinki-gan, a complex formulation of Japanese traditional herbal medicine, has been used widely and empirically to treat patients with lower urinary tract symptoms (LUTS), nocturia, feeling of incomplete empty and difficult voiding, predominantly related to benign prostatic hyperplasia (BPH). Recent animal studies have revealed that Gosha-jinki-gan increased bladder capacity and decreased the frequency of distension-induced rhythmic bladder contractions through the spinal kappa-opioid receptor, demonstrating that Gosha-jinki-gan could be effective for treatment of urinary frequency and urge incontinence⁵⁾. Some clinical studies have demonstrated the efficacy of Gosha-jinki-gan, frequently in conjunction with α 1-blocker or antimuscarinic drugs, for pollakisuria and nocturia associated with BPH and for LUTS mainly in males^{6,7)}. However, the number of patients in those reports was generally small, and the

objectives and definition of outcome adopted by the researchers were too varied. To date, no controlled clinical studies on the use of Gosha-jinki-gan with OAB have been published. The aim of this prospective study was to evaluate the efficacy and tolerability of a single-agent treatment with Gosha-jinki-gan in Japanese females with OAB through an objective analysis with three linguistically validated questionnaires: the International Prostate Symptom Score (I-PSS), I-PSS-QOL index, and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF).

MATERIALS AND METHODS

Patients who consulted our outpatient clinic with a chief complaint of OAB between October 2004 and May 2005 were considered for enrollment. All Japanese patients had evidence of OAB symptoms with no proven infection or other obvious pathology. Patients with neurogenic bladder disease were excluded. OAB was defined in accordance with the standardisation of terminology of the International Continence Society 2002¹⁾, and urge incontinence was defined as involuntary leakage accompanied, or immediately preceded, by urgency occurring more than once per week. The inclusion criteria were: 1) urgency once or more per week and increased daytime frequency exceeding 8 times per day, 2) an I-PSS total score of 8 or more points, and 3) an I-PSS-QOL index score of 3 or more points. Patients who had more than 100 ml of post-void residual urine (PVR) were excluded. Patients who had already taken medicine for OAB, for example anticholinergics or α 1-blocker, were also excluded. Full informed consent

about possible efficacy and adverse reactions of Gosha-jinki-gan was obtained from each patient before starting the study. Patients received a single-agent treatment with 7.5 g/day Gosha-jinki-gan orally for 8 weeks. No specific instructions about behavioral modification were given.

Before starting Gosha-jinki-gan, and then after the 8 weeks of administration, all patients were asked to count the number of voids during the daytime and during sleep for two days, and the I-PSS total scores and I-PSS-QOL index scores were examined. PVR was also evaluated by transabdominal ultrasonography before and after the administration. In addition, the ICIQ-SF was distributed to patients with urge incontinence (wet OAB) before and after the study. The efficacy assessment was done by comparing the QOL scores after 8 weeks of administration to those at the baseline. Outcome was measured as excellent (decrease of the QOL index by four or more points), improved (decrease of the QOL index by three to one point), unchanged (no change of the QOL index score), or worsened (increase of the QOL index by one or more points). Patients with excellent or improved outcome were defined as responders, and patients with unchanged or worsened outcome as non-responders. All patients were divided into a subgroup with dry or wet OAB. The therapeutic difference between these subgroups was examined retrospectively. Tolerability of the treatment was assessed by medical interview at every visit to the outpatient clinic to determine adverse events. Adverse reactions to Gosha-jinki-gan were also elucidated carefully. Statistical analyses were undertaken using the non-parametric Mann-Whitney U-test and Wilcoxon signed rank test, with $P < 0.05$ considered to indicate statistical significance.

RESULTS

1. Efficacy and tolerability of Gosha-jinki-gan

A total of 44 patients diagnosed as having OAB (aged 51 to 83 years, mean 66.8 ± 15.3 years) met the criteria and were evaluated. Prevalence rates of OAB without and with urge incontinence were 63.6 and 36.4%, respectively. Objective evaluation with the QOL questionnaire yielded a result of excellent in 3 patients (6.8%), improved in 20 (45.5%), unchanged in 18 (40.9%), and worsened in 3 (6.8%). Our results demonstrated that Gosha-jinki-gan was effective in 23 (52.3%) of the 44 patients. Adverse reactions to the treatment were observed in 4 (9.1%) of the patients; gastric discomfort in 2 patients, nausea in one and loose bowels in one. All adverse reactions were slight and were followed up closely without therapy. No patients discontinued the treatment due to these adverse events.

2. Urinary symptoms

After treatment, the I-PSS total scores and I-PSS-QOL scores were significantly reduced (Table 1). Fig. 1 shows the changes in each individual symptom of I-

PSS before and after 8-week administration. The number of voids during the daytime and during sleep was also significantly decreased. PVR were not significantly increased (10.7 ± 15.0 ml (range; 0–40 ml) pretreatment v.s. 8.0 ± 12.0 ml (range; 0–48 ml) at 8 weeks of administration).

3. Comparison between wet OAB and dry OAB

Comparison of patients showing dry OAB with those showing wet OAB revealed excellent and improved QOL in 67.9 and 25.0% respectively, the difference between the two groups being significant ($p < 0.01$) (Table 3). Comparison of the dry OAB and wet OAB showed significant difference in age between the two subtypes ($p = 0.0002$). The decrease in ICIQ-SF total scores in the wet OAB group was, of course, not significant (11.6 ± 2.7 pretreatment v.s. 9.8 ± 3.1 at 8 weeks of administration).

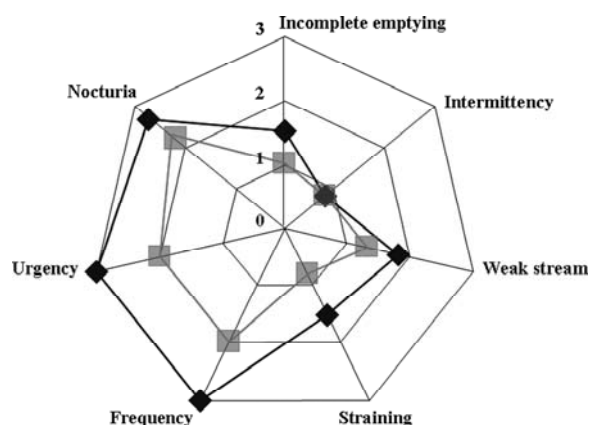
DISCUSSION

Our data indicate that the single-agent treatment with Gosha-jinki-gan for Japanese females with OAB significantly reduced the number of void during the daytime and the I-PSS total scores, resulting in the improvement of QOL in 52.3% of the patients. The fact that OAB greatly affects QOL of the patient leads to the strategy that the disorder should be treated appropriately. Anticholinergic drugs (Oxybutynin, Propiverine, Tolterodine and Solifenacin) have been regarded as a first-line treatment option for symptoms attributable to OAB. However, the utility of anticholinergic drugs is often limited by their high incidence of expected adverse reactions (dry mouth, central nervous dysfunctions, constipation, nausea, headache, dizziness and palpitation), which may result in poor compliance or even discontinuation of the drug treatment. Generally, Japanese traditional herbal medicines cause fewer adverse reactions than prescription drugs, often cost less, are available over-the-counter, and many have higher safety profiles than standard medical therapies⁸⁾. In traditional herbal medicine, LUTS are regarded as one urological pathological condition of structural and functional deterioration caused by growing old. Hachimi-jio-gan and Gosha-jinki-gan are popular herbal medicines frequently and empirically used for LUTS and related symptoms of BPH, according to the evidence of some clinical practices and not according to the evidence of clinical trials. Although most of the practices were conducted in small groups and of short duration, the results reported that Gosha-jinki-gan improves increased daytime frequency, nocturia and difficult voiding^{6,7)}. The success rates of Gosha-jinki-gan for various urinary symptoms associated with BPH/LUTS are reported to be 57.1–75.0%. However, most of the clinical data were obtained in conjunction with α 1-blocker and/or anticholinergic drugs. Tokunaga et al. reported that the effect of a single-agent therapy with Gosha-jinki-gan on pollakisuria and nocturia was 50 and 52.1% of patients with urinary disturbance, respec-

Table 1. Age, the total I-PSS scores, QOL index scores and urinary frequency in all patients before and after the single-agent treatment with Gosha-jinki-gan

Group n=44	Age (years)	I-PSS total scores (point)		QOL scores (point)		Urinary frequency (during the daytime)		Urinary frequency (during sleep)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
All patients n=44	66.8±15.3	14.2±4.9	10.0±6.0	4.2±0.7	3.1±1.3	9.3±1.8	7.8±1.7	2.7±1.7	2.2±1.7
		p<0.0001		p<0.0001		p<0.0001		p=0.0001	

(mean ± SD)

**Fig. 1.** Figure shows the changes in each individual symptom of I-PSS before and after 8-week administration.

tively⁷⁾. Our data from the single-agent therapy with Gosha-jinki-gan in females with OAB paralleled those results. Our results suggested that Gosha-jinki-gan might be more effective in females with dry OAB than wet OAB. However, there was a large age difference between the two subtypes. To elucidate the therapeutic profiles of Gosha-jinki-gan for dry and wet OAB, further studies which were adjusted for age would be required.

Gosha-jinki-gan occasionally causes adverse reactions (poor appetite, epigastric distress and diarrhea). The efficacy of drugs must be balanced against the adverse

reactions. The incidence observed in the study was low (9.1%) and those adverse reactions were all low- to moderate-intensity. No patients discontinued the treatment because of the adverse reactions, suggesting an excellent tolerability of Gosha-jinki-gan.

The mechanism of Gosha-jinki-gan for OAB has remained unclear. However, recent basic researches have gradually clarified the action mechanism of Gosha-jinki-gan for urinary frequency and urge incontinence⁵⁾. Gotoh et al. reported that the effects of Gosha-jinki-gan on urinary frequency are associated not with anticholinergic action but with inhibition of micturition reflex and diminishment of bladder sensation via the spinal kappa-opioid receptors, without inhibiting the amplitude of bladder contractions induced by electrical stimulation of the pontine micturition center⁵⁾. Gotoh et al. hypothesized that Gosha-jinki-gan could be effective for treatment of increased daytime frequency and urgency attributable to OAB⁵⁾. Our study supported the hypothesis.

Validated questionnaires are useful for recording symptoms, their frequency, severity and bother, and the impact of LUTS on QOL¹⁾. The I-PSS has subsequently been applied to evaluate LUTS in various conditions in men and women. It has been demonstrated that the I-PSS total scores among women are comparable to the scores among men in a clinical

Table 2. Age, the I-PSS total scores, QOL index scores and urinary frequency in dry OAB/wet OAB before and after the single-agent treatment with Gosha-jinki-gan

Group n=44	Age (years)	I-PSS total scores (point)		QOL scores (point)		Urinary frequency (during the daytime)		Urinary frequency (during sleep)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
Dry OAB n=28	61.2±16.4	13.1±4.7	7.9±5.0	4.3±0.6	2.6±1.2	9.3±2.2	7.7±1.9	2.3±1.8	1.5±1.4
		p<0.0001		p=0.0002		p<0.0001		p=0.0038	
Wet OAB n=16	76.7±5.2	16.1±4.6	13.8±6.0	4.1±0.8	4.1±1.1	9.3±1.1	7.9±1.5	3.5±1.4	3.4±1.5
	p=0.0002	p=0.0001		p=0.2568		p=0.0050		p=0.1317	

(mean ± SD)

Table 3. Clinical efficacy of Gosha-jinki-gan in patients with dry OAB and wet OAB

Group n=44	Responders		Non-responders		Response rate
	Excellent	Improved	Unchanged	Worsened	
Dry OAB n=28	10.7 (3)	57.1 (16)	25.0 (7)	7.1 (2)	67.9 (19) *
Wet OAB n=16	0 (0)	25.0 (4)	68.8 (11)	6.3 (1)	

(* p<0.01)

population⁹⁾ and the I-PSS can be used to evaluate the prevalence and severity of LUTS in females¹⁰⁾. The I-PSS-QOL index is a useful tool for assessing urinary problems as a first step¹¹⁾. ICIQ-SF is a brief and robust measure for evaluating the frequency, severity, and QOL impact of urinary incontinence¹²⁾. These three questionnaires may be reasonable tools to elucidate objectively and precisely the efficacy of Gosha-jinki-gan in females with OAB. However, overactive bladder symptoms score, which was a recommendable Japanese questionnaire, hereafter would be a useful tool to assess the detailed OAB symptoms in Japan²⁾.

The major drawbacks of this study are small number of patients, the lack of a placebo controlled group or active comparator, and no urodynamic data. In conditions of OAB which have a strong placebo component, the possibility of a placebo effect might be high. Therefore, conclusions for clinical efficiency of Gosha-jinki-gan might be seriously limited in scope. However, until now, our data may be the largest and first published demonstrating the safety, tolerability and efficacy of this therapy in females with OAB and the methods and evaluation of outcome followed the validated criteria.

In conclusion, our results from a prospective study demonstrate that Gosha-jinki-gan could be a safe and effective potential therapeutic alternative in females with OAB.

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和文抄録

女性過活動膀胱に対する牛車腎気丸の安全性と治療効果

梶原 充*, 牟田口和昭

中津第一病院泌尿器科

過活動膀胱の日本人女性に対する牛車腎気丸の安全性、効果を、西洋医学的アプローチでプロスペクティブに評価することを目的とした。44例（平均68歳）に牛車腎気丸を8週間投与し、排尿回数、IPSS、IPSS-QOL、残尿を評価。昼間排尿回数は有意に減少し、IPSSも有意に低下した。IPSS-QOLによる効果判定

では著効、有効、不変、悪化が7, 46, 41, 7%であった。副作用は9%であった。牛車腎気丸は安全で有用な治療オプションの1つとなりうることが期待される。

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* 現 : JA 尾道総合病院泌尿器科部長